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IN THE CANADIAN PATENT OFFICE

Examiner : M. Gillen
Applicant : Biogen, Inc.
Application No.: 374,378
Filed : April 1, 1981
For : DNA SEQUENCES, RECOMBINANT DNA
MOLECULES AND PROCESSES FOR PRODUCING HUMAN
FIBROBLAST INTERFERON-LIKE POLYPEPTIDES

AFFIDAVIT OF WALTER C. FIER

EXHIBITS 1-20

SUGANO EXHIBIT 1002
FIERS V. SUGANO
INTERFERENCE NO. 105,661

CURRICULUM VITAE		20	02
Opened / Déchettée le			
Walter Charles Cornelius FIER			
Date and place of birth: January 31, 1941, Leper, Belgium			
Nationality: Belgian		Commissaire des brevets	
Married; three children			
In presence of examiner / en présence de l'examineur			

1. Studies

High School: "Koninklijk Atheneum", Leper, 1949
 University: Faculty of Agricultural Sciences, Ghent:
 Engineer of Chemistry and Agricultural Sciences, 1954
 "Agrégé" for Higher Education (Biochemistry), 1960
 PhD, 1963

2. Scientific Career

1954 - 1955 Fellowship of the IWONL
 1956 Assistant, Laboratory of Physiological Chemistry, Faculty of Medicine, University of Ghent
 Fellowship of the Danish Government (Danish-Belgian Cultural Agreements)
 1957 - 1959 Research Assistant with the NFWO
 1960 - 1961 Research Fellowship from the Rockefeller Foundation, New York, USA
 1960 - 1961 Research Fellow in Biology, California Institute of Technology, Pasadena, CA, USA
 1960 - 1962 Senior Research Assistant with the NFWO
 1962 Research Associate, Institute for Enzyme Research, University of Wisconsin, Madison, WI, USA
 1963 Assistant Professor at the Faculty of Agricultural Sciences, University of Ghent, Belgium
 1967 Associate Professor at the Faculty of Sciences, University of Ghent, Belgium
 Responsible for the postgraduate course in Molecular Biology
 1967 Director-Head of the Laboratory of Molecular Biology, University of Ghent, Belgium
 1969 Professor of Molecular Biology at the Faculty of Sciences, University of Ghent, Belgium

3. Residences Abroad

Oct. 1, 1956 - Sept. 30, 1957
 Carlsberg Laboratory, Copenhagen, Denmark (with Prof. Dr. H. Holter)
 Oct. 1, 1960 - March 30, 1962
 California Institute of Technology, Department of Biophysics, Pasadena, CA, USA
 (with Prof. Dr. R.L. Sinsheimer)
 April 1, 1962 - Oct. 1, 1962, and May 1, 1963 - June 7, 1963
 Institute for Enzyme Research, University of Wisconsin, Madison, WI, USA (with Prof. Dr. H.G. Khorana)

This is EXHIBIT FIER-1
 to
 the Affidavit of Walter C. Fiers
 sworn before me
 this 4th day of November, 2001

Commissioner for Oath or Notary Public

4. Scientific Awards

- 1961 - Triannual Award "J.B. Van Helmon" (period 1958-1960) of the Royal Flemish Academy of Medicine of Belgium
- 1966 - Award of the Flemish Chemical Society (1964-1965)
- 1971 - Medal of the Société de Chimie Biologique de France
- 1975 - Award "Doctor A. De Leuw - Damry - Bourian" of the National Foundation for Scientific Research of Belgium for the period 1970-1975 (mathematical, physical and chemical sciences)
- 1976 - Francqui Award (Francqui Foundation, Belgium)
- 1978 - Doctor honoris causa, Catholic University of Leuven, Belgium
- 1980 - Jenkinson Memorial Lecture, University of Oxford, UK
- 1986 - Dr. Beijerinck Gold Medal for Virology, Royal Dutch Academy of Sciences, The Netherlands
- Rik & Nel Wouters Prize for Cancer Research, Belgium
- 1989 - Anois - Baillet Latour Prize, Belgium
- Carlos J. Finlay Prize (UNESCO Prize for Microbiology, including Immunology, Molecular Biology and Genetics)
- 1990 - Personal title of "Baron" and hereditary nobility conferred by H.M. the King of Belgium
- 1991 - Robert Koch Prize (Robert Koch-Stiftung, Bonn, Germany)

5. Memberships, Offices and Committee Assignments

- 1966 - Elected to the Council of the Belgian Biochemical Society
- Elected as a member of the European Molecular Biology Organization (EMBO)
- 1969 - Member of the Advisory Board of the "European Journal of Biochemistry"
- 1970 - Visiting professor at the Catholic University of Leuven, Belgium
- 1971 - Member of the European Association for Cancer Research
- Member of the Editorial Board of "Natuur en Techniek", The Netherlands
- 1972 - Chairman of the research group "Oncoviruses" (formed on behalf of the Higher Council against Cancer), Department of Health, Belgium
- Member of the Editorial Board of "Intervirology"
- Guest member of the Dutch "Working Group on Nucleic Acids" (SON)
- 1973 - Corresponding member of the Royal Academy of Belgium, Class of Sciences
- 1974 - Organizer of the EMBO Workshop "Restriction Enzymes and DNA sequences", De Cirkel, Drongen, Belgium
- Member of the International Scientific Committee of the "International Institute of Cellular and Molecular Pathology" (ICP), Brussels, Belgium
- Member of the Scientific Board of the Departments of Molecular Biology, ULB, Brussels, Belgium
- 1975 - Member of the Liaison Committee for Recombinant DNA Research of the European Science Foundation
- Member of the NFWO Commission for Biochemistry and Molecular Biology
- 1976 - Member of the Council for Medical Ethics, Foundation for Medical Scientific Research of Belgium
- 1977 - Member of the Editorial Board of "Gene"
- Member of the Scientific Council for Cancer Research of the ASLK
- Member of the Council of the European Molecular Biology Organization
- Member of the Overseas Advisory Panel of "The Biochemical Journal"

- 1978 - Second vice-presidents of the Belgian Biochemical Society
- 1979 - "Chaire Francqui" at the State University of Liège, Belgium
 - Member of the IUPAB Commission on Subcellular and Macromolecular Biophysics
 - Member of the Programme Committee for the 5th International Congress for Virology

- Member of the Editorial Board of "Biochimie"
 - Member of the Scientific Board of Biogen Inc.
- 1980 - Member of the Advisory Panel of the NATO Advanced Study Institutes
- 1981 - Member of the Royal Academy of Belgium, Class of Sciences
- 1982 - President of the Scientific Council for Cancer Research of the ASLK
 - Member of the Editorial Board of "The EMBO Journal"
 - President of the Belgian Biochemical Society
- 1983 - Member of the Editorial Board of "Nucleic Acids Research"
 - Member of the Editorial Board of "Anticancer Research"
 - Commander in the Order of Leopold
- 1984 - Member of the National Committee for Biochemistry
- 1985 - President of the NFWO Commission for Biochemistry and Molecular Biology (until 1990)
- 1987 - Member of the Commission for Biotechnology, Flemish Council for Science Policy
 - Member of the Editorial Board of "Biotherapy"
- 1988 - Member of the FEBS Fellowship Committee
 - Member of the Editorial Board of "The European Journal of Immunology"
 - Member of the Editorial Board of "Molecular Biology Reports"
 - Member of the Editorial Board of "Biotechnology Therapeutics"
 - Member of the Editorial Board of "Methods in Molecular and Cellular Biology"
 - Member of the Cell Board Subcommittee of the "Medical Research Council" (UK)
 - Member of the EEC Study Group on Ethical, Social and Legal Aspects of the Predictive Medicine Programme
- 1989 - Member of the Editorial Board of "Cytokine"
 - Member of the "Academia Europaea"
 - Elected member of "The Human Genome Organisation" (HUGO)
 - Member of the Board of the "Foundation van Gysel for Medical Research"
- 1990 - President of the Scientific Council for Cancer Research of the ASLK-Insurances
 - Corresponding member of the "American Association for Cancer Research"
 - Member of the Scientific Steering Committee for the EMBL (appointed by the Flemish Executive)
 - Belgian representative to the Council of the "International Society for Interferon Research" (ISIR)
 - Civil Cross First Class
- 1991 - Member of the "Scientific Advisory Committee" (SAC) for the EMBL (appointed by the EMBL Council)
 - Member of the Editorial Board of "Cancer Communications"
 - Honorary member of the Royal Flemish Society of Engineers
 - Member of the Scientific Board of the "Institut Pasteur du Brabant"
- 1992 - Member of the Editorial Board of "International Journal of Oncology"
 - Member of the Scientific Council of the "International Institute of Cellular and Molecular Pathology" (ICP), Brussels, Belgium
 - Honorary member of the Royal Academy of Medicine of Belgium
 - President of the "4th International Congress on Tumor Necrosis Factor and Related Cytokines", organized in Veldhoven, The Netherlands

"Chaire Franquet" at the Catholic University of Louvain (KUL), Faculty of Medicine, Belgium

1994 - *Member of the Editorial Board of "Circulatory Shock"*

1995 - *Member of the Editorial Board of "Lymphokine and Cytokine Research"*

- *Member of the Editorial Board of "Natural Immunity"*

- *Member of the Editorial Board of "The Journal of Inflammation"*

1996 - *Grand Officer in the Order of the Crown*

- *Retired as Professor at the University of Ghent and became Professor emeritus*

- *Director of the VIB (Flanders Interuniversity Institute for Biotechnology),
Department of Molecular Biology*

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Dec 30	20 02
Walter FIERS	
<i>[Signature]</i>	
Commissioner of Patents Commissaire des brevets	
<i>[Signature]</i>	
Deputy Commissioner of Patents Deputy Commissioner of Patents	

LIST OF PUBLICATIONS

- A. Research papers
- B. Short communications
- C. a. Books (contributed chapters, editorships)
b. Reviews concerning own research
c. General (molecular biology, virology, etc.)
- D. Abstracts

This is EXHIBIT FIERS-2
to
the Affidavit of Walter C. Fiers
sworn before me
this 19th day of November, 2001

Commissioner for Oath or Notary Public
Board Assigned Page #121

- A.22 MIN JOU, W. and PIER, W.
Studies on the bacteriophage MS2. VII. Structure
determination of the longer polynucleotide sequences
present in the pancreatic ribonuclease digest of the
viral RNA.
J. Mol. Biol. 40, 187-201, 1969.
- A.23 DE WACHTER, R. and PIER, W.
Sequences at the 3'-terminus of bacteriophage Q β RNA.
Nucleic Acids Res. 11, 222-235, 1983.
- A.24 WILLIS, E., DE ROVER, J.C. and PIER, W.
The factor-dependence of bacteriophage Q β RNA-
polymerase.
Arch. Intern. Physiol. Biochem. 77, 548-550, 1969.
- A.25 SIEGERS, H. and PIER, W.
Studies on bacteriophage MS2. VIII. Evidence for
direct formation of MS2 RNA by reaction with
formaldehyde at acidic pH.
Biopolymers 8, 1373-1389, 1970.
- A.26 DE WACHTER, R. and PIER, W.
Fractionation of RNA by electrophoresis on
polyacrylamide gel slabs.
Biochem. Biophys. Res. Commun. 48, 148-151, 1972.
- A.27 CROSS, H.J., DIERCKX, F.B. and PIER, W.C.
The RNA glycoproteinase activity of *Escherichia*
coli. A study on substrate specificity.
Eur. J. Biochem. 17, 116-123, 1970.
- A.28 HADJIAN, G., MIN JOU, W. and PIER, W.
Studies on the bacteriophage MS2. IX. The
heptanucleotide sequence present in the pancreatic
ribonuclease digest of the viral RNA.
J. Mol. Biol. 57, 597-615, 1971.
- A.29 DE WACHTER, R., VANHOVEN, A., MIRRECAERT, J.,
and PIER, W.
The leader sequence from the 3'-terminus to the A-
protein initiation codon in MS2-virus RNA.
Proc. Natl. Acad. Sci. USA 68, 203-208, 1971.
- A.30 DE WACHTER, R., MIRRECAERT, J., VANHOVEN, A.,
CONTERAS, R. and PIER, W.
Studies on the bacteriophage MS2. The untranslated
5'-terminal nucleotide sequence preceding the first
cistron.
Eur. J. Biochem. 22, 409-411, 1971.
- A.31 DE WACHTER, R. and PIER, W.
Preparative two-dimensional polyacrylamide gel
electrophoresis of 32P-labeled RNA.
Anal. Biochem. 49, 194-207, 1972.
- A.32 MIN JOU, W., SIEGERS, H., DE WACHTER, R. and PIER, W.
Nucleotide sequence of the gene coding for the
bacteriophage MS2 coat protein.
Nature 237, 82-88, 1973.
- A.33 REHAUT, E. and PIER, W.
Studies on the bacteriophage MS2. X. The
termination signal of the A protein cistron.
J. Mol. Biol. 71, 211-241, 1972.
- A.34 VANHOVEN, A., DEHAUT, E., VAN HOVEN, W. and PIER, W.
Studies on the bacteriophage MS2. XI. Suppressor-
sensitive mutants of the A protein cistron.
Mol. Gen. Genet. 117, 359-370, 1972.
- A.35 VERBAAR, E. and PIER, W.
Studies on the bacteriophage MS2. XII. Expansion of
the virus in the host.
Virology 50, 810-820, 1972.
- A.36 CONTERAS, R., ISHERART, M., MIN JOU, W. and PIER, W.
Bacteriophage MS2 RNA: Nucleotide sequence of the end
of the A protein gene and the intergenic region.
Nucleic Acids Res. 1, 97-101, 1973.
- A.37 SIEGERS, H. and PIER, W.
Studies on the bacteriophage MS2. XIII. Contamination
of MS2 RNA in acid medium.
Biopolymers 12, 1207-1208, 1973.
- A.38 SIEGERS, H. and PIER, W.
Studies on the bacteriophage MS2. XIV. Fixation of
the MS2 RNA acid structure by formaldehyde.
Biopolymers 12, 2073-2083, 1973.
- A.39 SIEGERS, H., CLAUSSE, J. and PIER, W.
Studies on the bacteriophage MS2. XV. Hydrolytic
properties of the active end acid MS2 RNA structure.
Biopolymers 12, 2083-2088, 1973.
- A.40 HADJIAN, G. and PIER, W.
Studies on the bacteriophage MS2. An internal
nucleotide frequent coexisting with ribosomal binding
sites.
Eur. J. Biochem. 26, 129-132, 1973.
- A.41 VOLCKAERT, C. and PIER, W.
A simple and highly sensitive method for sequence
determination of 32P-labeled nucleic acids.
Anal. Biochem. 62, 312-323, 1974.
- A.42 VAN DE WOUDE, A., ROCIERA, A., VAN HEMERCKE, J.,
VAN HOOVEN, H., VOLCKAERT, C. and PIER, W.
Genomic nucleotide substitutions: A new technique for
sequence analysis of RNA.
Mol. Acids Res. 1, 1059-1065, 1974.
- A.43 CONTERAS, R. and PIER, W.
A method for the isolation of cytoplasmic RNA from
bacteriophage T1-infected cells.
Anal. Biochem. 67, 319-328, 1975.
- A.44 VAN, C., VAN, A., VAN, C., VAN, C., VAN, C., VAN, C.,
Location of the coat protein gene in the MS2
virus genome.
Virology 64, 240-243, 1975.

- A.43 VANDEBERGHE, R., MIN JOU, W. and PIERA, W.
3'-terminal nucleotide sequence (p - 315) of bacteriophage MS2 RNA.
Proc. Natl. Acad. Sci. USA 73, 3328-3332, 1976.
- A.44 PIERA, W., CONTRERAS, R., GUERINCK, F., HADENHAM, G., MURCHART, J., MIN JOU, W., RAYNAUDIER, A., VOLCHART, G., TALAERT, M., VAN DE KENCKHOVE, J., WOLF, P. and VAN MONTAGU, M.
A-protein gene of bacteriophage MS2.
Nature 256, 213-216, 1975.
- A.45 DEVOS, R., GILLIS, E. and PIERA, W.
The mycotic addition of poly(A) to the 3'-end of RNA of the bacteriophage MS2 and to a model system.
Eur. J. Biochem. 83, 401-410, 1978.
- A.46 YANG, R.C., VAN DE VOORDE, A. and PIERA, W.
Restriction map of the 3'-terminal 40 bases by the restriction endonuclease III of *Mycobacterium* mycophilum.
Eur. J. Biochem. 81, 101-117, 1978.
- A.47 YANG, R.C., VAN DE VOORDE, A. and PIERA, W.
Specific cleavage and physical mapping of the 3'-terminal 40 bases of the bacteriophage MS2 RNA by the restriction enzyme.
Eur. J. Biochem. 81, 119-126, 1978.
- A.48 VOLCHART, G., MIN JOU, W. and PIERA, W.
Analysis of 31P-labeled bacteriophage MS2 RNA by a mini-sequencing procedure.
Anal. Biochem. 73, 433-436, 1976.
- A.49 PIERA, W., CONTRERAS, R., GUERINCK, F., HADENHAM, G., MURCHART, J., MURCHART, A., VAN DER KENCKHOVE, J., VOLCHART, G., TALAERT, M., VAN DE KENCKHOVE, J., WOLF, P. and VAN MONTAGU, M.
RNA primary and secondary structure of the replicase gene.
Nature 268, 302-307, 1976.
- A.50 VAN ROY, F. and PIERA, W.
Mycoplasma in African Green Monkey kidney cell cultures: biochemical detection and effects in virus-infected cells.
In Vitro 13, 337-343, 1977.
- A.51 DEVOS, R., VAN MONTAGU, J., RAYNAUDIER, G., MURCHART, J., MIN JOU, W., RAYNAUDIER, A., VOLCHART, G., TALAERT, M., VAN DE KENCKHOVE, J., WOLF, P. and VAN MONTAGU, M.
Addition of 31P RNA adenylylation (p - 315) to bacteriophage MS2 or 3'-linked poly(A) to bacteriophage MS2 RNA and its effect on RNA replication.
Biochim. Biophys. Acta 487, 219-227, 1978.
- A.52 MIN JOU, W. and PIERA, W.
Studies on the bacteriophage MS2. XVIII. Cooperation of the noncoding sequence in related bacteriophage genes.
J. Mol. Biol. 108, 301-309, 1976.

- A.53 VAN DE VOORDE, A., CONTRERAS, R., MURCHART, J. and PIERA, W.
The initiation region of the MS2 RNA genome.
Cell 9, 117-120, 1976.
- A.54 VOLCHART, G., CONTRERAS, R., SOLESA, E., VAN DE KENCKHOVE, J., MIN JOU, W., RAYNAUDIER, A., VOLCHART, G., TALAERT, M., VAN DE KENCKHOVE, J., WOLF, P. and VAN MONTAGU, M.
A-protein gene of bacteriophage MS2.
Nature 256, 213-216, 1975.
- A.55 KERNER, R. and PIERA, W.
A two-dimensional electrophoretic procedure for the separation of RNA restriction fragments.
J. Mol. Biol. 110, 101-104, 1977.
- A.56 VANDEBERGHE, R., THYS, F., VAN DE VOORDE, A. and PIERA, W.
Restriction sequence of the restriction fragment Hind III.
Nucleic Acids Res. 5, 1007-1011, 1978.
- A.57 MIN JOU, W., VAN MONTAGU, M. and PIERA, W.
On the parallel modeling of the MS2 RNA.
Biochem. Biophys. Res. Commun. 77, 1003-1007, 1978.
- A.58 ELTON, R. A. and PIERA, W.
Restriction variations in the MS2 RNA sequence in bacteriophage MS2.
J. Theoret. Biol. 61, 69-78, 1978.
- A.59 DEVOS, R., VAN MONTAGU, J., GILLIS, E. and PIERA, W.
Synthesis of MS2 RNA by bacteriophage MS2 RNA polymerase of bacteriophage MS2 RNA polymerase in vitro.
Eur. J. Biochem. 75, 219-222, 1977.
- A.60 CONTRERAS, R., VOLCHART, G., THYS, F., VAN DE VOORDE, A. and PIERA, W.
Nucleotide sequence of the restriction fragment Hind III - Eco RI of MS2 RNA.
Nucleic Acids Res. 6, 1003-1011, 1978.
- A.61 VAN MONTAGU, M., VAN DE VOORDE, A. and PIERA, W.
Nucleotide sequence of the MS2 RNA restriction fragment Hind III - Eco RI.
Nucleic Acids Res. 6, 1011-1012, 1978.
- A.62 VOLCHART, G. and PIERA, W.
Restriction variations in the MS2 RNA sequence in bacteriophage MS2.
Anal. Biochem. 81, 219-222, 1977.
- A.63 VOLCHART, G. and PIERA, W.
Micro in vitro assay for rapid sequence analysis of 31P-labeled MS2 RNA: Double digestion and pancreatic ribonuclease analysis.
Anal. Biochem. 81, 228-236, 1977.

- [illegible]

- A.109 SCHWARTZ, R., VAN DERKAMP, J. and FIERSE, W.
Specific binding of interferon (IFN) to
cellular receptors in human fibroblasts
isolated from the fibroblast binding site
Proc. Natl. Acad. Sci. USA 78, 1311-1316, 1981.
- A.110 CONTRERAS, R. and FIERSE, W.
Initiation of transcription by RNA polymerase II in
permeabilized, SV40-infected or noninfected, CV1 cells.
Mol. Cell. Biochem. 8, 213-216, 1981.
- A.111 TAVENIER, J., DIERCKX, B. and FIERSE, W.
The gene for a unique human fibroblast interferon
cDNA is transcribed from a single intervening
sequence.
Mol. Cell. Biochem. 8, 211-213, 1981.
- A.112 REMAUT, E., STAMSIENS, P. and FIERSE, W.
Plasmid vectors for high-efficiency expression
controlled by the pL promoter of coliphage lambda.
Gene 15, 81-83, 1981.
- A.113 VAN DERKAMP, J., FIERSE, W. and FIERSE, W.
Phosphorylation patterns of tumor antigens in cells
infected with or transfected by SV40 virus (SV40).
J. Virol. 40, 28-31, 1981.
- A.114 FANG, R., NIP JOU, W., NUTTERMECK, D., DEVOS, R. and
FIERSE, W.
Complete structure of SV40/DNA/RNA influence
hepatocellular carcinoma virus as progenitor of
human H3 Hong Kong 1988 influenza hemagglutinin.
Cell 25, 115-122, 1981.
- A.115 VAN DERKAMP, J., NIP JOU, W., NUTTERMECK, D., DEVOS, R.
and FIERSE, W.
Complete nucleotide sequence of the nucleocapsid
gene from the human influenza virus H3N2/8/34
(H3N2).
Eur. J. Biochem. 119, 317-322, 1981.
- A.116 DEBRAYE, W., DIERCKX, B., TAVENIER, J., NUTTERMECK, D.
and FIERSE, W.
Nucleotide sequence of the choriocapsid gene for human
fibroblast (H3) interferon and of the flanking
regions.
Gene 15, 137-143, 1981.
- A.117 VOLTAERT, G., TAVENIER, J., DIERCKX, B., DEVOS, R.
and FIERSE, W.
Molecular mechanisms of nucleotide sequence
correspondence in cDNA clones of human fibroblast
interferon genes.
Gene 15, 219-222, 1981.
- A.118 CHEN, C., CHEN, D. and FIERSE, W.
Small RNA synthesis in Escherichia coli of the SV40
labeled RNA polymerase control of the bacteriophage
Gene 15, 15-24, 1981.
- A.119 CHEN, C., CHEN, D., DIERCKX, B., and FIERSE, W.
Hypocytosine alteration of the nucleotide sequence
affecting the translation initiation codon and the
affect on bacterial expression of the cloned SV40
small RNA gene.
Gene 15, 55-63, 1981.
- A.120 REMAUT, E., DE NACHT, P., NUTTERMECK, D., STAMSIENS,
P. and FIERSE, W.
Functional expression of individual plasmid-coded RNA
bacteriophage M13 genes.
EMBO J. 1, 185-188, 1981.
- A.121 KATZ, R. A., REMAUT, E., FIERSE, W. and VAN DERKAMP,
J.
SV40 gene expression of RNA phage M13 depends on a
protein during translation of the overlapping coat
protein gene.
Mol. Cell. Biochem. 15, 1-11, 1981.
- A.122 CHEN, C. and FIERSE, W.
Expression and secretion of human fibroblast (H3)
interferon in monkey cells after transfection with a
recombinant SV40 plasmid vector.
J. Mol. Appl. Genet. 1, 185-194, 1981.
- A.123 GOSWAMI, N. and FIERSE, W.
Translational control in prokaryotic genes: the
applied codon-anticodon interaction energy and the
effect of codon usage on efficiently expressed genes.
Gene 15, 199-209, 1981.
- A.124 COMPTON, J., DE VIT, L., FIERSE, W., DIERCKX, B., DE
FIERSE, E. and FIERSE, W.
Secretory proteins induced in human fibroblasts under
conditions used for the production of interferon.
Proc. Natl. Acad. Sci. USA 78, 1312-1317, 1981.
- A.125 DEVOS, R., CHEN, D., FIERSE, W., TAVENIER, J., VAN
DERKAMP, J., NIP JOU, W. and FIERSE, W.
Molecular cloning of human genome interferon cDNA and
its expression in eukaryotic cells.
Mol. Cell. Biochem. 10, 145-150, 1981.
- A.126 TAVENIER, J., DEVOS, R., TAVENIER, J., CHEN, D.,
CHEN, C. and FIERSE, W.
Cloning and structure of the human genome interferon
cDNA.
EMBO J. 1, 551-558, 1981.

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R.18p1e, efficient in vitro synthesis of capped RNA
needed for direct expression of cloned autoraytic
genes. *Nucl. Acids Res.* 10, 6333-6361, 1982.
- A.128 CONTRERAS, R., CHENOUTRE, B., DEGRAVE, M., VAN DE
VOORDE, A. and FIERS, W.
Evidence for the direct involvement of RNA
polymerase I in the synthesis of late SMC RNA.
Nucl. Acids Res. 10, 508-516, 1982.
- A.129 VAN ROPPE, L., MIR JON, M., HUYLBERG, D. and
FIERS, W.
Complete nucleotide sequence of a human influenza
neuraminidase gene of subtype H1N1/Victoria/77/77.
J. Mol. Biol. 161, 3-11, 1982.
- A.130 VAN ROPPE, L. and FIERS, W.
Metabolic turnover of phosphatidylcholine in human
virus 48 large T antigen.
J. Virol. 41, 642-648, 1982.
- A.131 CHENOUTRE, B., VAN ROPPE, L. and FIERS, W.
Changes in gene expression and protein
phosphorylation in murine cells transformed or
abortively infected with wild type and mutant Simian
virus 40.
J. Biol. Chem. 258, 5276-5280, 1983.
- A.132 DE GROOTE, G., DE WAZE, P., VAN DE VOORDE, A., DE
ROOY, W. and FIERS, W.
Use of monoclonal antibodies to detect human
placental alkaline phosphatase.
Clin. Chem. 29, 115-119, 1983.
- A.133 CHENOUTRE, B., TSKO, W. and FIERS, W.
Improved plasmid vectors with a thermostable
expression and temperature-regulated runaway
replication.
Gene 23, 101-112, 1983.
- A.134 CHENOUTRE, B., VAN DE VOORDE, A., CONTRERAS, R., VAN
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Simian virus 40 mutants carrying extensive deletions
in the early region.
J. Virol. 42, 1-14, 1983.
- A.135 SCHILL, A.J., DEVOS, A., VAN DER HEIJN, J. and
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Expression and characterization of the product of a
human leukemia interferon cDNA gene in Chinese hamster
ovary cells.
Proc. Natl. Acad. Sci. USA 80, 6891-6896, 1983.
- A.136 POORE, J.E., GIBSON, M.A., COOPER, R.A., REISS,
C.E., BUCKWOLD, S.J., FIERS, W. and AULT, R.A.
Isolation by vesicular endocytosis in inducible by
activated T cells and by human T interferon.
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- A.137 PERKIN, J., JOHNSON, T.C., BUCHHA, P.V., HOLTE, C.,
BRADY, S. and FIERS, W.
Colon usage and differentiation in vivo and in vitro
of the H2A coat protein gene.
J. Biol. Chem. 258, 10007-10011, 1983.
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Human virus 48 large T antigen: induction of
differentiation in human cells by T antigen-induced cells.
Nucl. Acids Res. 11, 161-168, 1983.
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HUYLBERG, D. and FIERS, W.
Complete nucleotide sequence of the influenza B
virus/77/77 virus hemagglutinin gene and
comparison with the H1N1/40 hemagglutinin.
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D. ABSTRACTS

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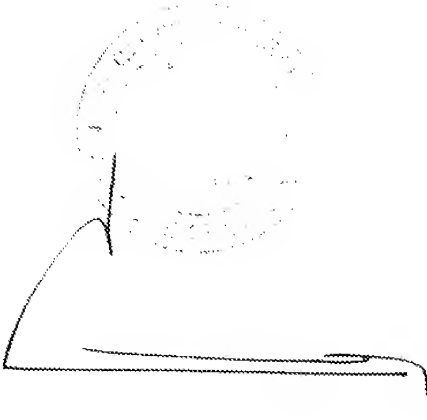
Dec 30 2002

[Signature]

Notary Public
Notaire Public

[Signature]

Notary Public
Notaire Public



This is EXHIBIT FIER-3
to
the Affidavit of Walter C. Fiers
sworn before me
this 14th day of November, 2001

Commissioner for Oath or Notary Public

Dergack hkl

21/4/

- Guanyliniumchloride . 4 ml gelaten op 1 ml Gd } RNA of 1

- Zinner IF $2-3 \times 10^8$ U / mg.

mens, mens -

mens: all fibrillat - type

Zinnering - poly D - glucose

affigel met zeefde uitdied.

→ gel { 35 K
22 K

reloading 85% 35 K.

mit most uitif bid. mabele.

longgel: 2% wavy - 2 lippe bollen

fingerprint gelif.

Zinner: portinissel ok

onticellulose uit oftef.

- Spec. bolon : 2 - delect of 1 -

{ Fit
line.

2. Blo. seque.

- Bolon. Kanten iatimale : geen vertis v. stitit

- Kanten : 1 touwgeen / met van dufin.

- Glycosylatie PAS (pratie uit - sliff).

Reager 35 K +

22 K -

longgel : 3 reusamistie belanden → 1 bolon (IEFI.

Cor A - colun : nersiff 2 gelon -

Tunicangon : niets men neerland → glycosylati

by glycosylatie mit vertueel van bid act.

Angen cellu heelt men glycosylati neetf volletij
te eliminer door tunicangon belandling.

Kodimale : vertis v. bid act v. Fit-IF
men misien te beestind.

- Inductie : poly I:C + HEAT-behandeling → past on nagen.

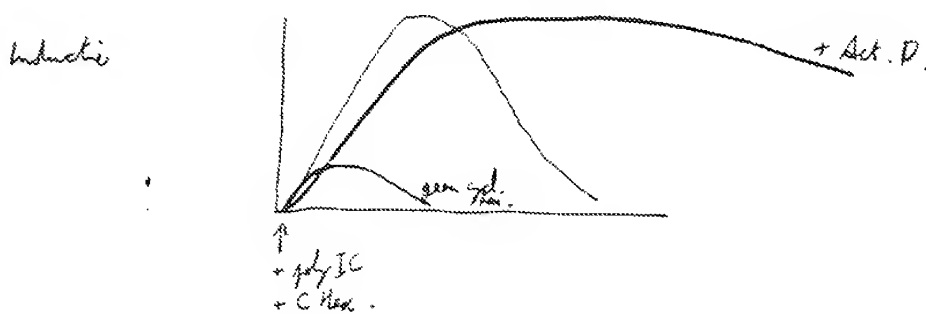
- Productie : Kankers : niet ook fibr. 3-20%
 Fibr. : " " " " 1-20% (lang af p. menen v. infectie)

human interferon: specifiek.
 gezond v. stimulatie v. Thymus.

poly I:C + polybryne : weinig nevenwerkingen - kan als behandeling aan patiënten toegepast worden.

- mRNA : transcriptie - meer → X. basis.

Revel : ook in retic. - minder 100%



Onderzoek : 4 firma's Score 1
 6 groepen. -

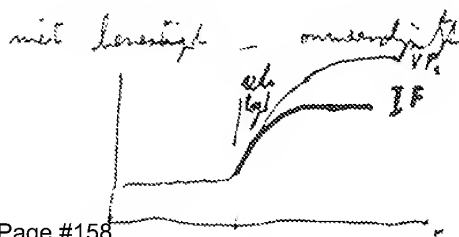
- chromosom : receptoren 21
 productie: 2, 3 - ook van 21!

- receptoren : licht actief. - binding van gebeld IF
 membranveranderingen in IF behandelde cellen.

- anticellulair effect : medicijn celgroei - niet veranderig. morfologie
 effect in G1.

- effect of tumornieuw : vermindering extracellulair virusel ontz.
 vermindering intracellulair - defect op nucle

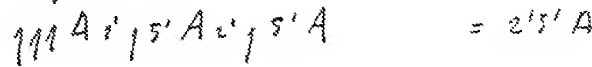
- Revel : effect of uncoupling?
 IF 10u na infectie.



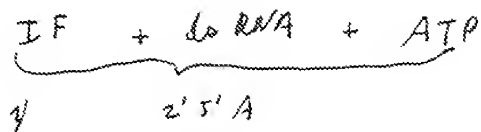
III but 6x higher intense methylation -
 and are cap -

cellular and noncoding.

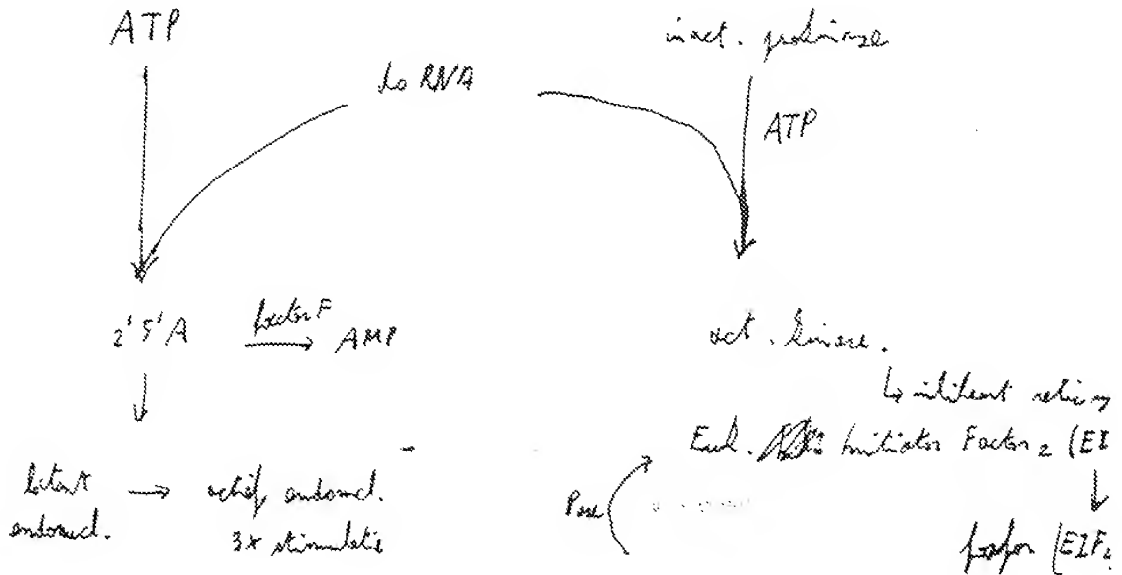
- Effect in cell-free system.



cell-free system :



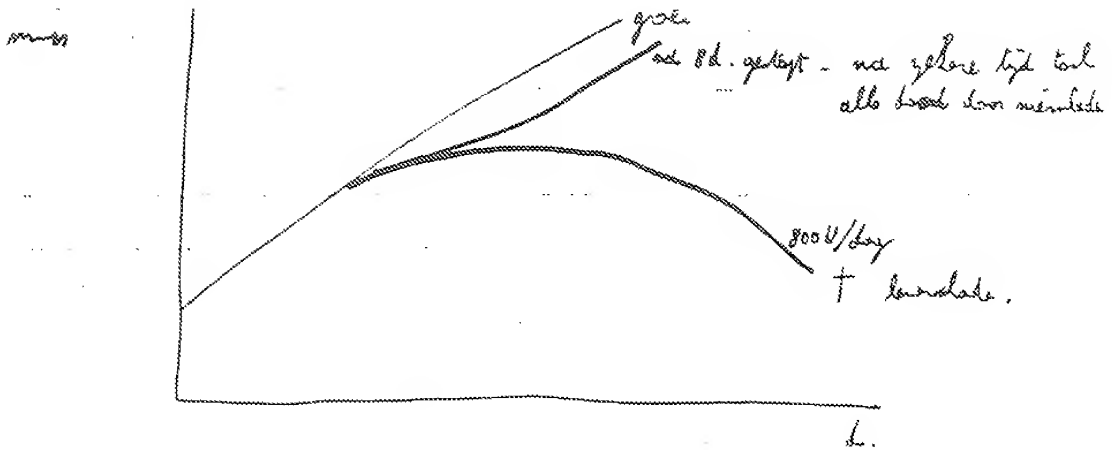
2) kinase \rightarrow { Euk Factor 2.
 histone



{ ERNA
 methylation

phases & not oxygen

- Clinical: 2'5' A not in normal cells - homologous 5x down IF
 L 1270 \rightarrow L 1280 B (IF resistant - hyper receptor)
 \downarrow \downarrow
 tumor tumor
 IF generally IF \rightarrow cell culture - therapy resistant



mens $2-5 \times 10^5$ U/kg.

neel trials, men 99% leucocytes -

+ Hayes ty oog.

overheet geen positief effect inder and andere behandeling (bv. steroïden!).

- Ebola

- Hepatitis B -

- Osteosarcoma. Stomach.

verlozing 15-65-75%

Steroïden kunnen mogelijk zijn
Wat op kleine kinderen.
Kiezen men sensitief.

Namals: - IF - is equivalent aan leucocytes.

Fibrinolyt: {
mestisypulatie
hepatitis B
oog hepatitis

{ fibrinolyt : geen level.
leucocytes : mel "

Namensatjueh: loots : onguiraleton?

via proteoglycine?

deling is bloedend (minder met FIF)

BIUGEN S.A.

Opened <u>Dec 30</u> 20 <u>02</u>
Déclaré le <u>[Signature]</u>
Commissioner of Patents Commissaire des brevets
In presence of examiner <u>[Signature]</u> en présence de l'examineur

Reply To
Suite 3700
One New York Plaza
New York, New York 100

December 1, 1978

Prof. Dr. W. Fiers
Laboratorium voor
Moleculaire Biologie
9000 Ghent
BELGIUM

Dear Dr. Fiers:

This will confirm our meeting at 8 o' clock a.m. in Ghent on Thursday, December 14. I will have with me Deborah Masters who is one of Biogen's vice presidents. We will meet you at the Ghent railway station. We need to take a 11 o' clock train from Ghent in order to catch the 11:43 a.m. train to Paris.

I look forward to seeing you on the 14th.

Sincerely,

[Signature]
Daniel D. Adams
President &
Managing Director

DDA:bjb



This is EXHIBIT FIERS-4
to
the Affidavit of Walter C. Fiers
sworn before me
this 19th day of November, 2001

Commissioner for Oath or Notary Public

11b Avenue de la Porte-Neuve, Luxembourg

2R3

9/2, 1979

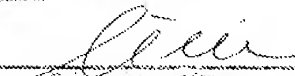
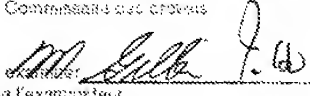
11th

BIOGEN

SCIENTIFIC BOARD MTG. (PARIS)

Robin Nicholson
Ken Murray
Bernard Mach
Ray Schaeffer
Moshe Abafi
Bob Lucianno
Wally Gilbert

Charles Weissmann
Peter Hans Hofschneider
Heinz Schaller
Walter Fiers
Dag Laurason
Brian Hartley
Philippe Kourilsky
Phil Sharpe

Opened	Dec 30	20 02
Decaschétée in		
		
Commissioner of Patents Commissaire aux brevets		
In presence of examiner		
en présence de l'examinateur		



This is EXHIBIT FIER5-5
to
the Affidavit of Walter C. Fiers
sworn before me
this 19th day of November, 2001

Commissioner for Oath or Notary Public

WALTER FIER'S

done \Rightarrow collaboration w/ 2 other
groups

1- in Leuvenne

Desomer no longer active

exp. in assay for Interf.
prepare cells - running bioassays

2- Comteut

Pasteur Institute of Brussels
all translation work.

- Mol. Biol - w/ Fier's group in Ghent

Start of fibroblast RNA - gradient \rightarrow
partial purif. - $\sim 40 \times$ purif.

~ 150 clones most screening on this disc.
then 20,000 clones

Using dADT tails (disables
compared to C.W. work) - higher
level of trans formation - \therefore used this for
higher yields.

* Techniques / ^{cloning} same as Chen. Weinman

Detection & screening:
Hybrid Assisted Translation --
wanted to be less dependent on
posit. artifacts.

System has not worked - despite
apparent functioning of controls -

Assays -

① Orig - same as C.W. -
same tech. by content in Bursall

②: Peticularly ~~Dr.~~
ass. biol. activity

Much more active in #1 than #2 (20x)

Screened 150 clones in groups of 50 -
mixed results.

HAT - -

out of protein = same whether
or not you melt it. - see that system works.

Satellite Tobacco Necrosis Virus
(STNV) is used as marker. (?)

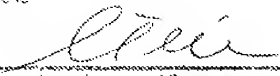
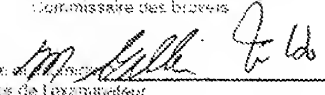
Goat anti-interferon ~~also~~
bring down ~~the~~ STNV.

very good messenger
in terms of activity

either exp. works or

interf. or induces in mysterious way

Screening 20,000 in groups of 50

Opened	Dec 30	2002
Detachée le		
 Notary Public of Ontario Commissaire des brevets		
In presence of	 en présence de l'examinateur	



This is EXHIBIT FIERS-6
to
the Affidavit of Walter C. Fiers
sworn before me
this 19th day of November, 2001

Commissioner for Oath or Notary Public

- De positieve resultaten op DBM-culturen zijn zeer duidelijk, ook op herhaling (tabel van B).

Gel ④ bevat ook kolom 13, die nogal twijfelachtig positief bleef. nu ook duidelijk ③.

- De keuze van vroege groepselike valt op C.

- ③ op cellulose (2x).
- ③ op biologische afvalrest. (plaque reduction assay is minder goed verlichting tot geslacht)
- ③ op Sefhane → andere afvalrest
→ dit koloniegewende DMSO is vroege gewende
gewende tot suiker gewende.
(op cellulose is: bevat nog erg veel RNA)
- zijn enkele maal ③ gekoörd!

C = 2'12 (A→D) - 46 bloem

1. opvoeren van laag 2'12 op dish - 16 bloem/bet.

2. enten van pre-kultuur 16/bet

$A_2 \rightarrow C_1$	$\left[\begin{array}{l} A_2 \rightarrow C_1 \\ C_2 \rightarrow D_{12} \end{array} \right]$
$C_2 \rightarrow D_{12}$	

3. enten van 400 ml kulturen 16/bet

$A_2 \rightarrow C_1$	$\left[\begin{array}{l} A_2 \rightarrow C_1 \\ C_2 \rightarrow D_{12} \end{array} \right]$	\rightarrow (tot 9 x 8)
$C_2 \rightarrow D_{12}$		

4. lyse-procedure

na afcentrifugeren vd kulturen (GS-3, 10 mm - 3000 fm) (3x per pot)
2x wasen met 1x TES

terugspinnen in 100 ml suikrose 10% - Tis 50 mM pH 8
+ 10 ml lysozyme (50 mg/ml Tis 25 mM pH 8) (± 30 min)
+ 10 ml EDTA (10.5M pH 8)
- 80 ml TLR (over de middag)

alles bij
keluutemperatuur.

Clearing spin : 6 poly-allomies (4x12) gr groep (103 groepen)
24 K - 45 mm.

5. PEG.-precipitate : SN van Clearing spin + 1/3 vol 40% PEG
2M NaCl

overnacht in ijskoude kamer (ijs of ijs)



2. was 1
3. was 2
4. eluke

→ geen oepufek plakken!

Het invieren nl pellets (na opgraven) is mislukt de oorzaak van de aanwezigheid van RNA in de DNA-preparaten na lye en Cell product-centrifugatie!

C - subgroepen

2¹-12

C₁: A₂ → A₉ (8)

C₂: A₁₀ → A₁₁, B₁ → B₆ (8)

C₃: B₇ → B₁₂, C₁ (7)

C₄: C₂ → C₉ (8)

C₅: C₁₀ → C₁₂, D₁ → D₅ (8)

C₆: D₆ → D₁₂ (7)

7. CoCl_2 -verminderd-gedroogte centrifugate (2 per groep, totaal 12)

RFOT.
40K
15°C
over weekend.

→ banden goed per herday - onduidelijk
vrij Rv12

8. Aftappen met epuraatke punkte → 5 ml tevens spuit

IAA extractie:
+ 3 vol H_2O
+ 1/10 vol NaAc 2M pH 5.1
+ 2 vol EtOH.

overnacht -20°C

9. EtOH pettes afdrainen

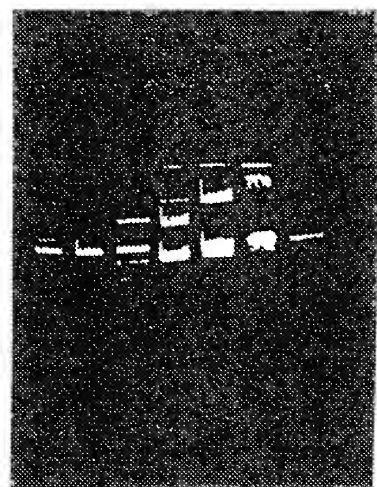
heropnemen in 1/10 STE
fensolieren - fensolam warmen
etherextractie 3x
ether verdampen

tot vol per groep - 1 ml 1/10 STE

→ 2 μl op gel laden (1% opaan)
+ 1 μl pBR 322 referentie.

10. Suikrose-methylenblauw-gradient-centrifugate

→ wegen afwezig zijn de RNA
⇒ NIET NODIG



SUBGROEPEN C

1 2 3 4 5 6
↓
pBR-322 referentie
↓
⇒ 0.3 0.3 0.4 ± 1 μg 1 0.1 0.2

$$O_2 : A_{10} \rightarrow A_{11}, B_1 \rightarrow B_6 \quad (6)$$

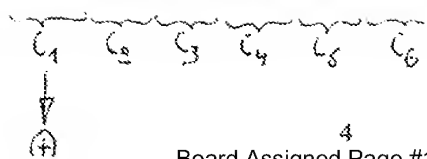
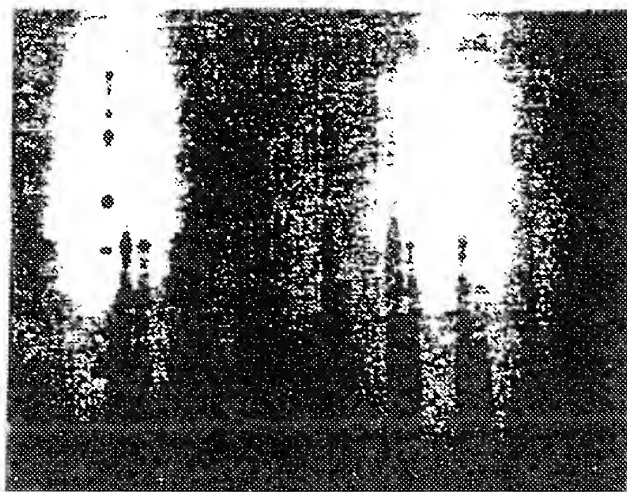
$$O_3 : B_1 \rightarrow B_{12}, C_1 \quad (7)$$

$$O_4 : C_2 \rightarrow C_5 \quad (8)$$

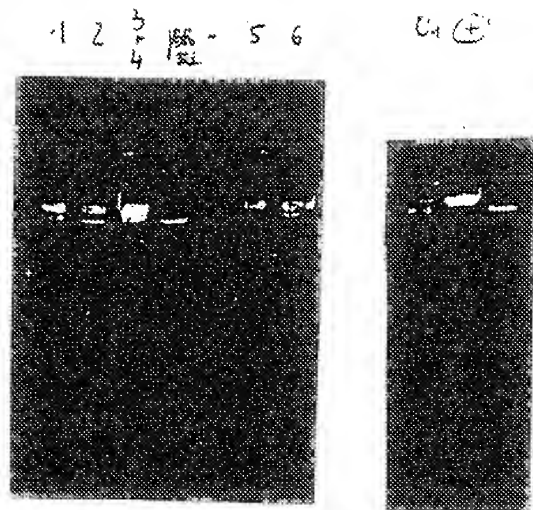
$$O_5 : C_{10} \rightarrow C_{12}, D_1 \rightarrow D_5 \quad (9)$$

$$O_6 : D_6 \rightarrow D_{12} \quad (10)$$

Rezultati na kolonijbnici



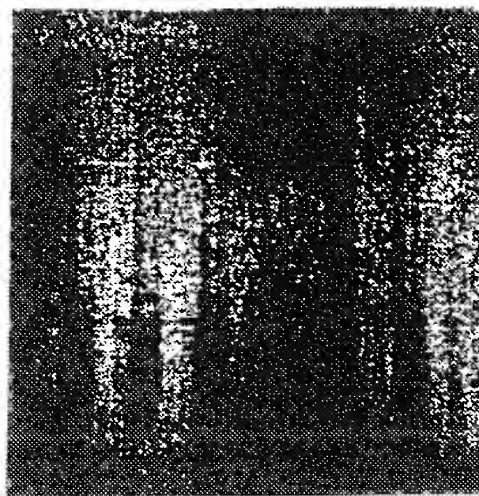
SUBGROEPEN 0



→ 14pg 13 19 (10) 12 13 10 13 (10pg)

Er is een weinig RNA aanwezig (→ 3+4 schijnen geven een plek, sen v
afant echter niet meer)

3,4,5 bevatten chromosomaal DNA.



0₁ 0₂ 0₃ 0₄ 0₅ 0₆

gekineerd STNV-RNA

→ 7H worm-gel

[3,4. → jukteel-banden , STNV-RNA na CIP-behandeling.
(calc-intestine-phosphatax)
5,6,7,8,9 → jukteel-banden , STNV-RNA, zonder voorbehandeling.
(In geachte-rijgorde).

24/11

RNA bereidingen (Raga - Leiden)

W_1 : non induced	VGS # 23, 10 vollen	(10 10 79)
W_2 : induced	VGS # 24, 20 vollen	(24 10 79)
W_3 : induced	VGS # 26, 15 vollen	(16 11 79)

↳ overgebracht als EtOH precipitaat.

* afcentrifugeren 9000 tpm HB4 -20°C

heropnemen TE + 0.1% SDS. 400 µl

+ 1 vol $CHCl_3$ / IAA

+ 1 vol fenol en fenolfase nauwzetten met 50 µl TE.

SN 400 + 50 potten en nauwzetten met 1 vol $CHCl_3$ / IAA
(verwijderen van fenol)

* EtOH precipitatie

↓

27/11

heropnemen in 600 µl TE, 0.1% SDS.

↓ -20°C

2 µl maatlijn, OD meten.

W_1 : 0.101	$\times 2 \times 100 \rightarrow 20.2$	OD/ml	$\times 0.6 \rightarrow 12.12$	OD	$\times 40 \rightarrow$	485
W_2 : 0.144		22.8	OD/ml		11.98	OD
W_3 : 0.150		30.0	OD/ml		18.00	OD

individueel in batches

W_1	$3 \times 170 \mu g$
W_2	$4 \times 20 \mu g + 4 \times 115 \mu g$
W_3	$4 \times 30 \mu g + 4 \times 132 \mu g$

↳ alles EtOH precipitatie i.v. 0.27 NaAc, pH 5.1

1/17/80



10/4/80

DSH - allentone ~ DNA

hybridisatie met plopp
0.05%

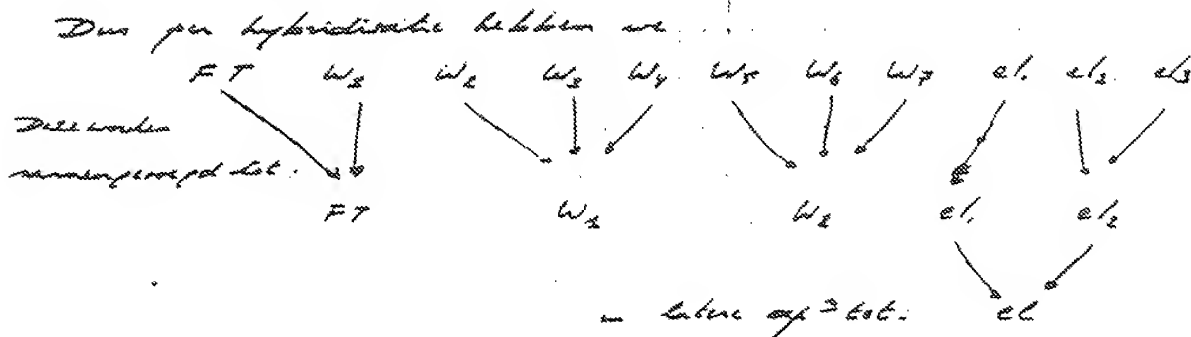
hybridisatie oornacht

daarna 7x wassen

3x elutie

alles gebeurt batchwijze in effluentie per centrifugatie

Dec 30 1980
Opraven
Dacachetee la
STNT-RNA
Commissioner of Patents
Commissaire des brevets
In presence of
en présence de l'examinateur



hierby is FT: donker
W. was
el. sluit

Alle fracties worden na namenvolgen en vóór
ethanol precipitatie ~~namen~~ benoemd in 1 helft

(A) 1/2 → precipitatie met halfleer RNA

(B) 1/2 → " poly A⁺ RNA (andere soort)



This is EXHIBIT FIERS-7
to
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sworn before me
this 19th day of November, 2001

afkomstig van over het geleend RNA. $\frac{5}{13}$ $\frac{12}{14}$ $\frac{2}{2}$
 full size (355-6p) van fractie 13 op gel 57 kolommen } C
 12014 op gel 23 kolommen } G
 medium size (750-850bp) van fr. 13 op gel 8 kolommen } G

Screening

16 prepen van 8 46 clones, afkomstig van puriteit -prepara
 RNA met titel 2.5

120	88	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	positief - negatief met de DNA	
																		prepar	
																		Biol. g. n. k.	Actief
																		16 K.	Actief

V.B. 10.1.11 van 16 K. kunnen we een duidelijk beeld
 hebben welke prepen positief of negatief zijn
 1 van biologische activiteit betekent een detecteerbare
 eten in FT niet dat de prep negatief is van kind u
 Zo word C bijvoorbeeld enkel als positief gedetecteerd
 bij herhalingen
Beant zowel C als O zijn positief op kind akt 16 K
 Ben G zijn zeker ook positief op 16 K

Tandemmassen spectrometer

Er wordt samen geanalyseert met analyseprogramma

C_2 \rightarrow 26k

O_2 \rightarrow 26k

O_1 \rightarrow mol. akt. IF.

	O_2	C_2	
		aanleiding	aanleiding
1	1	FR 26	FR 26
2	2	0.1 0	+
3	3	0	-
4	4	0	-
5	5	0	-
6	6	0	-
7	7	0	-
8	8	0	-
9	9	0	-
10	10	0	-
11	11	0	-
12	12	0	-
13	13	0	-
14	14	0	-
15	15	0	-
16	16	0	-
17	17	0	-
18	18	0	-
19	19	0	-
20	20	0	-
21	21	0	-
22	22	0	-
23	23	0	-
24	24	0	-
25	25	0	-
26	26	0	-
27	27	0	-
28	28	0	-
29	29	0	-
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31	31	0	-
32	32	0	-
33	33	0	-
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37	37	0	-
38	38	0	-
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40	40	0	-
41	41	0	-
42	42	0	-
43	43	0	-
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45	45	0	-
46	46	0	-
47	47	0	-
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84	84	0	-
85	85	0	-
86	86	0	-
87	87	0	-
88	88	0	-
89	89	0	-
90	90	0	-
91	91	0	-
92	92	0	-
93	93	0	-
94	94	0	-
95	95	0	-
96	96	0	-
97	97	0	-
98	98	0	-
99	99	0	-
100	100	0	-

NA
Geen analyse van O_2 en C_2 omdat de analyse van O_1 niet mogelijk was. Het is niet mogelijk om te zien hoe het met de analyse van O_1 samenhangt.

Besluit $C_2/4$ en $O_2/2$ zijn identiek 26k. punt

O_1 is nog te analyseren

analyseprogramma

26 k. analyse van O_1 is niet mogelijk. Het is niet mogelijk om te zien hoe het met de analyse van O_1 samenhangt.

O₂ subproof

Biologische Aktivität

<i>clone</i>	<i>of 280-act. pilot</i>		<i>of 280-act. pilot</i>		<i>of auto-cultured pilot</i>	
	<i>FT</i>	<i>OL</i>	<i>FT</i>	<i>OL</i>	<i>FT</i>	<i>OL</i>
<i>O₂ 12</i>	<i>0.2</i>	<i>0</i>	<i>0.7</i>	<i>0</i>	<i>2.0</i>	<i>0</i>
<i>2</i>	<i>2.2</i>	<i>0</i>	<i>0.2</i>	<i>0</i>	<i>0.7</i>	<i>0</i>
<i>3</i>	<i>2.2</i>	<i>0</i>	<i>2.2</i>	<i>1.2</i>	<i>2.0</i>	<i>0</i>
<i>4</i>	<i>2.2</i>	<i>0</i>	<i>2.0</i>	<i>0</i>	<i>2.2</i>	<i>0</i>
<i>5</i>	<i>0.7</i>	<i>0</i>	<i>0.7</i>	<i>2.2</i>	<i>2.2</i>	<i>0</i>
<i>6</i>	<i>0.7</i>	<i>0</i>	<i>2.0</i>	<i>2.2</i>	<i>0.5</i>	<i>0</i>
<i>7</i>	<i>0.5</i>	<i>0</i>	<i>2.2</i>	<i>0</i>	<i>2.2</i>	<i>0.2</i>
<i>8</i>			<i>2.2</i>	<i>2.2</i>	<i>2.2</i>	<i>0.7</i>
<i>O₂ auto-cultured</i>	<i>2.2</i>	<i>0.5</i>	<i>2.2</i>	<i>2.2</i>		

Dem O₂ 12 is ebenfalls positiv von IF-Aktivität.

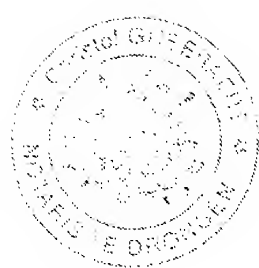
Dec 30

02

[Signature]

M. G. L. J. H.

en présence de l'examinateur



This is EXHIBIT FIERS-8
to
the Affidavit of Walter C. Fiers
sworn before me
this 9th day of November, 2001

Commissioner for Oath or Notary Public

after SDS-polyacrylamide gel electrophoresis, the eluate should be centrifuged at 20,000 rev/min (Sorvall SS-34 rotor) for 20 minutes to remove particulate matter before dialysis. Coomassie blue staining of the gels to locate protein bands does not interfere with subsequent sequencer analysis.

New technologies such as the improved amino acid sequencing method described above lead to new research opportunities. With the greater sensitivity provided by this technique, we now can obtain amino acid sequence information on both proteins and peptides with submicrogram (picomole) quantities. This sensitivity should permit analysis of biomedically relevant molecules—such as the interferons—that can only be obtained in microgram quantities, and this ability opens possibilities for further study of these molecules. For example, knowledge of the amino acid sequence permits the synthesis of corresponding DNA probes and opens the possibility of

new strategies for isolating genes, such as those for interferons, that express low levels of messenger RNA's (8).

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9. Supported by a gift from the Ben Weingart Foundation.

29 November 1979

Human Fibroblast Interferon: Amino Acid Analysis and Amino Terminal Amino Acid Sequence

Abstract. The purification of human fibroblast interferon has been simplified to a one-step procedure consisting of affinity chromatography on Blue Sepharose and sodium dodecyl sulfate polyacrylamide gel electrophoresis. A preliminary amino acid composition and the sequence of the 13 amino-terminal residues of homogeneous interferon prepared by this method is reported.

Since the discovery of interferon, its purification and chemical characterization have been primary goals of interferon research. Although their attainment has been slow because of the small quantities of interferon proteins avail-

able, purification to homogeneity has now been achieved with some interferons. However, only microgram quantities have been available for characterization—human fibroblast interferon (1, 2), human lymphoblastoid interferon (3), human leukocyte interferon (4), mouse interferon (5)—and only limited structural information has been acquired (4, 6).

A thorough understanding at the molecular level of the numerous phenomena that are caused by interferon in cells in culture and in animals will not be possible until the elucidation of primary and secondary structures of the interferon proteins is achieved. This structural information will permit (i) comparison of amino acid sequences of interferons from various cell types and animal species, (ii) identification of the polypeptide segments involved in binding to interferon-specific cell-surface receptors, and (iii) chemical synthesis of interferons.

We now report an improved procedure for the purification of human fibroblast interferon that can be used to provide enough protein for structural studies.

Using the automated protein micro-sequencing technique described in (7), we have determined the sequence of the 13 amino acid residues at the amino terminus of the interferon prepared by this method. We also report a preliminary amino acid composition of the protein.

Human diploid fibroblast cells (HS-4) were cultured and interferon was produced (1). Interferon was assayed by a microtechnique (8) with vesicular stomatitis virus as the challenge virus. Interferon units are given in National Institutes of Health human fibroblast interferon units.

The crude interferon, 10 to 15 liters produced in the absence of serum, was made 1M in NaCl and passed at room temperature through a column (4 by 10 cm) of Blue Sepharose (Pharmacia, Inc.) equilibrated with 0.02M sodium phosphate buffer, pH 7.2, containing 1M NaCl. The interferon was retained whereas more than 95 percent of the total protein passed through the column. The interferon was eluted with a mixture of the column buffer and ethylene glycol (1:1), and each fraction was diluted immediately with 0.5 volume of the buffer (Fig. 1a). Fractions containing interferon activity were pooled, diluted with two volumes of the column buffer, and passed through a small (1 by 6 cm) Blue Sepharose column for concentration. The interferon was eluted as described above (Fig. 1b).

Fractions containing interferon were pooled, dialyzed against 1 mM Tris-HCl,

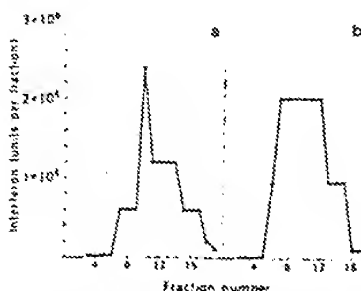


Fig. 1. (a) Fractionation of crude interferon on a large column of Blue Sepharose. Elution of interferon with 50 percent ethylene glycol in column buffer begins at fraction 1. (b) Small Blue Sepharose column. Fractions 7 to 17 in (a) were pooled, passed through the small column, and eluted with 50 percent ethylene glycol in column buffer (fractions 1 to 20).

Table 1. Amino acid composition of human fibroblast interferon.

Amino acid	Composition	
	Mole percent	Residues per 20,000 daltons
Asp	11.1	18.9
Thr	4.0	6.8
Ser	6.2	10.5
Glu	15.9	27.0
Pro	1.6	2.7
Gly*	4.6	7.8
Ala	5.9	10.0
Cys†	1.0	1.7
Val	3.5	6.0
Met	1.7	2.9
Ile	5.3	9.0
Leu	12.0	20.4
Tyr	4.4	7.5
Phe	5.5	9.4
His	2.9	4.9
Lys	8.8	15.6
Arg	6.4	10.9
Trp‡	0.6	1.0

*Includes correction for free glycine present in undiluted protein. †Determined after performic acid oxidation. ‡Determined after hydrolysis with mercaptoethanesulfonic acid.

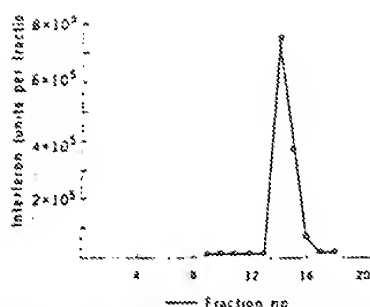


Fig. 2. (a) Preparative electrophoresis of interferon activity profile. Fractions 6 to 15 in Fig. 1b were pooled, concentrated, and subjected to electrophoresis in a polyacrylamide slab gel, 0.75 mm thick. Fractions 14 and 15 were pooled and processed for amino acid sequencing. (b) Polyacrylamide slab gel, staining of proteins eluted from preparative gel in (a). Approximately 2 percent of the protein in fractions 14 and 15 (a) was subjected to electrophoresis and stained. Lanes 1 and 3, standard proteins; lane 2, interferon.

pH 6.8, containing 0.02 percent sodium dodecyl sulfate (SDS, Bio-Rad electrophoresis grade), and concentrated to dryness in a vacuum centrifuge. The interferon was then subjected to electrophoresis on a SDS-polyacrylamide slab gel and eluted (Fig. 2a). Fractions eluted from the gel were assayed for interferon activity (Fig. 2b). Approximately 0.2 μ g of interferon from the peak activity fraction was subjected to electrophoresis in this system again, and the gel was stained with Coomassie blue (Fig. 2b).

The preparative electrophoresis fractions containing interferon were pooled and centrifuged for 30 minutes at 30,000 rev/min at 4°C to remove polyacrylamide gel particles. The interferon solution was dialyzed first against 0.15M NaCl containing 0.1 percent SDS and then against 0.02 percent SDS. The dialyzed interferon was concentrated to dryness in a vacuum centrifuge.

This purification procedure is simpler and shorter than that described previously (1). Recoveries from the large Blue Sepharose column have ranged from 50 to 100 percent, and those from the small column approach 100 percent. The interferon (5×10^5 U/mg) eluted from these columns is stable for at least 4 weeks at 4°C in 0.1M NaCl, 35 percent ethylene glycol, pH 7.2. Recoveries of activity from the SDS gels have ranged from 5 to 20 percent, and specific activities of this protein have ranged from 2×10^5 to 8×10^5 U/mg. Accurate specific activities are difficult to determine, and

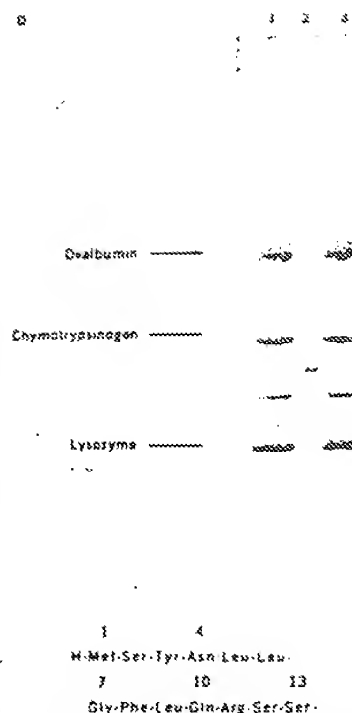


Fig. 3. The amino-terminal amino acid sequence of human fibroblast interferon.

two- to fourfold differences above 1×10^5 U/mg are probably not meaningful. Overall yields of purified interferon from 10- to 15-liter batches of crude material (5×10^5 to 7×10^5 total units, 8×10^5 U/mg) have averaged around 10 percent. This gives 5 to 10 μ g of homogeneous interferon.

Amino acid analysis on 1- to 2- μ g portions was performed on a Durrum D-500 amino acid analyzer (Table 1). Automated Edman degradation on 0.4- to 2- μ g portions of the purified interferon was performed on a spinning cup sequencer (7). Phenylthiohydantoin (PTH) amino acids were identified by high-performance liquid chromatography (HPLC) on a Du Pont Zorbax CN column (9).

The sequence of the 13 amino terminal amino acid residues of human fibroblast interferon was determined by this microsequencing technique (Fig. 3). Yields of PTH methanamine at cycle 1 for three sequencer runs ranged from 60 to 100 percent (based on protein determination by amino acid analysis), and the sequencer repetitive cycle yields were 92 to 95 percent. Any unblocked minor peptide sequence present at > 5 percent of the reported sequence could have been detected by the methods used, but none has

homogeneity of the interferon peptide preparation.

Determining the amino acid sequence of a protein is essential in order to identify its active site and to understand its molecular mechanism of action. Comparison of structural features of interferons from different species and from different cell types within an animal can prove or disprove whether they are different proteins. If there is an active site common to all interferons, it should be identifiable by comparison of the amino acid sequences. Comparison of the amino terminal sequence reported here for human fibroblast interferon does not as yet reveal any apparent homology with the amino-terminal sequence reported for human lymphoblastoid interferon (10). However, there is limited homology (3/13 residues identical) with the 37,000 dalton mouse Ehrlich ascites cell interferon (11).

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